Antibiotics for community acquired lower respiratory tract infections (LRTI) secondary to Mycoplasma pneumoniae in children (Review)

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[Intervention Review]

Antibiotics for community acquired lower respiratory tract infections (LRTI) secondary to Mycoplasma pneumoniae in children

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ABSTRACT

Background

Mycoplasma pneumoniae (*M. pneumoniae*) is widely recognised as an important cause of community-acquired lower respiratory tract infection (LRTI) in children. Pulmonary manifestations are typically tracheobronchitis or pneumonia but *M. pneumoniae* is also implicated in wheezing episodes in both asthmatic and non-asthmatic individuals. Although antibiotics are used to treat LRTI, a review of several major textbooks offers conflicting advice for the use of antibiotics in the management of *M. pneumoniae* LRTI in children.

Objectives

To determine whether antibiotics are effective in the treatment of childhood LRTI secondary to *M. pneumoniae* infections acquired in the community.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2005, issue 1), which contains the Acute Respiratory Infection Group's Specialized Register; MEDLINE (1966 to February 2005); and EMBASE (1980 to December 2004).

Selection criteria

Randomised controlled trials comparing antibiotics commonly used for treating *M. pneumoniae* (i.e. macrolide, tetracycline or quinolone classes) versus placebo, or antibiotics from any other class in the treatment of children under 18 years of age with community acquired LRTI secondary to *M. pneumoniae*.

Data collection and analysis

The authors independently selected trials for inclusion and assessed methodological quality. Relevant data were extracted and analysed separately and any disagreements were resolved by consensus.

Main results

A total of 1352 children were enrolled from six studies. The number of children from one study was unavailable. Data interpretation was significantly limited by the inability to extract data that specifically referred to children with *M. pneumoniae*. Clinical response did not differ between the children randomised to a macrolide antibiotic and the children randomised to a non-macrolide antibiotic. There were no studies comparing relevant antibiotics with placebo.

Authors' conclusions

This review found insufficient evidence to draw any conclusions about the efficacy of antibiotics for LRTI secondary to *M. pneumoniae* in children. The use of antibiotics for *M. pneumoniae* LRTI has to be individualised and balanced with possible adverse events associated with antibiotic use. There is a need for high quality, double-blinded randomised controlled trials to assess the efficacy and safety of antibiotics for LRTI secondary to *M. pneumoniae* in children.

PLAIN LANGUAGE SUMMARY

There is insufficient evidence from trials about the benefits of antibiotic treatment for lower respiratory tract infections in children secondary to *Mycoplasma pneumoniae (M. pneumoniae).*

M. pneumoniae is an bacterial infection often responsible for lower respiratory tract infections (LRTI) in children. The infection can present in a number of different ways and the most common respiratory manifestations are acute bronchitis, pneumonia or exacerbation of asthma. The illness is generally self-limiting with symptoms lasting several weeks. Antibiotics are often given to children with *M. pneumoniae* LRTI but the authors found there were no adequate trials which show that antibiotics are effective.

BACKGROUND

Description of the condition

Mycoplasma pneumoniae (M. pneumoniae) is widely recognised as an important cause of community acquired lower respiratory tract infection (LRTI) in children, accounting for 14% to 34% of cases (Kogan 2003; Michelow 2004; Nelson 2002; Principi 2002). The highest attack rates are reported to occur in 5 to 20-year-olds and the infection is usually self-limiting with symptoms lasting several weeks (Nelson 2002; Rudolph 2003). More recently *M. pneumoniae* has been identified as an important cause of LRTI in children less than five years of age (Principi 2001). Pulmonary manifestations are typically tracheobronchitis or pneumonia but can be complicated by pleural effusion, lung abscess, pneumothorax, bronchiectasis and respiratory distress syndrome (Principi 2002). *M. pneumoniae* is also implicated in wheezing episodes in both asthmatic and non-asthmatic individuals (Phelan 1994; Principi 2001). Extrapulmonary manifestations may include erythema multiforme, myocarditis, encephalitis, Guillain-Barre Syndrome, transverse myelitis and haemolytic anaemia (Nelson 2002; Waites 2003). Radiographic findings are quite variable and non-diagnostic (Principi 2001). In some cases there can be significant radiological changes in the absence of clinical signs on auscultation of the chest (so-called 'walking pneumonia') (Rudolph 2003).

Description of the intervention

Antibiotics are frequently used to treat LRTI and empiric antibiotic therapy is often chosen to cover both bacteria and atypical organisms (Kogan 2003). A review of several major textbooks offers conflicting advice for management of *M. pneumoniae* LRTI. The chapter on *M. pneumoniae* in a paediatric respiratory textbook (Phelan 1994) mentions that there is little evidence of beneficial effect from antibiotic therapy. This is in contrast to the recommendations in a major general paediatric textbook (Rudolph 2003) and paediatric infectious disease textbook (Katz 1998) which states that erythromycin is the treatment of choice.

Why it is important to do this review

The conclusion that antibiotics are effective in *M. pneumoniae* chest infections seems to have been drawn from trials of antibiotic therapy for community acquired or atypical pneumonia, where

M. pneumoniae was identified as a causative organism in a subgroup of cases. In these studies, macrolide antibiotics, to which *M. pneumoniae* is susceptible, have been compared to non-macrolide antibiotics. However, it is not always possible to draw meaningful conclusions from the results, as the numbers of individuals with *M. pneumoniae* are small in most trials (Block 1995; Kogan 2003; Wubbel 1999).

Identification of *M. pneumoniae* infection as the causative infectious agent may, however, pose difficulties. Serological tests are the most common method used to diagnose *M. pneumoniae* infections, but can lead to difficulties with interpretation (Principi 2001). Measurement of immunoglobulin M (IgM) is used to diagnose acute infection, but the accuracy of the test depends on the method used. Not all methods are specific for IgM and an elevated IgM may persist for months after the acute infection (Murray 2003). Immuno-fluorescent antibody (IFA) assay is more sensitive and specific than the complement fixation (CF) test (Murray 2003; Principi 2001). Identification of *M. pneumoniae* in nasopharyngeal secretions by culture or polymerase chain reaction (PCR) may also cause difficulties with interpretation as this organism can persist for variable periods following the acute infection (Murray 2003). The 'gold standard' for diagnosis of *M. pneumoniae* infection is a four-fold increase in total antibody titre as measured in paired sera (Katz 1998; Murray 2003).

OBJECTIVES

To determine whether antibiotics are effective in the treatment of childhood LRTI secondary to *M. pneumoniae* infections acquired in the community.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing antibiotics from the macrolide, tetracycline or quinolone class versus placebo, or antibiotics from any other class.

Types of participants

All trials that included children under 18 years of age with community acquired LRTI secondary to *M. pneumoniae*. Diagnosis of *M. pneumoniae* infection was via either a four-fold rise in total antibody titre from paired sera or total antibody titre $\geq$ 1:512 on a single specimen. Other methods of diagnosis such as culture or PCR of *M. pneumoniae* in nasopharyngeal secretions or demonstration of elevated IgM on a single specimen (IgM titre $\geq$ 1:10) were included, and analysed separately as a subgroup

Exclusion criteria:

(a) children with underlying chronic cardiorespiratory illnesses such as cystic fibrosis, bronchiectasis, immunodeficiency, chronic neonatal lung disease and symptomatic congenital heart disease;

(b) children with non-community acquired LRTI.

Types of interventions

All randomised controlled trial (RCT) comparisons of antimicrobials from the macrolide, tetracycline or quinolone class, versus placebo or other antibiotics in the management of LRTI.

Two separate treatment regimes were evaluated:

(a) any antibiotic versus placebo; and

(b) antibiotics from the macrolide, tetracycline or quinolone class versus placebo, or antibiotics from any other class.

Trials that included the use of other medications or interventions in addition to antibiotic therapy were included if all participants had equal access to such medications or interventions.

Types of outcome measures

Attempts were made to obtain data on at least the following outcome measures:

Primary outcomes

- proportions of participants who were not improved at follow up. (Failure to improve will be measured according to the hierarchy listed below 'secondary outcomes'.)

Secondary outcomes

- mean difference in symptoms and signs (mean improvement in clinical state);
- proportions requiring hospitalisation;
- proportions experiencing pulmonary complications (empyema, pleural effusion, air leak);
- proportions experiencing non-pulmonary complications;
- proportions experiencing adverse effects (for example nausea, diarrhoea, abdominal pain, rash);
- proportions experiencing complications (for example requirement for medication change).

The proportions of participants who failed to improve on treatment and the mean clinical improvement were determined using the following hierarchy of assessment measures. All outcomes were reported but where two or more assessment measures are reported in the same study and conflicting results are obtained, the outcome measure that was listed first in the hierarchy was used.

1. Objective measurements of cough indices (cough frequency).
2. Symptomatic (cough, wheeze, dyspnoea, malaise, general well being, headache) - assessed by the child (Likert scale, visual analogue scale, level of interference of symptoms, diary, quality of life).
3. Symptomatic (cough, wheeze, dyspnoea, malaise, general well being, headache) - assessed by the parents/carers (Likert scale, visual analogue scale, level of interference of symptoms, diary, quality of life).
4. Symptomatic (cough, wheeze, dyspnoea, malaise, general well being, headache) - assessed by the clinician (Likert scale, visual analogue scale, level of interference of symptoms, diary, quality of life).
5. Fever.
6. Non-clinical outcomes (chest radiology, white cell count, C-reactive protein, erythrocyte sedimentation rate, lung function).
7. Eradication of *M. pneumoniae* by PCR evaluation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2005, issue 1), which contains the Acute Respiratory Infection Group's Specialized Register; MEDLINE (1966 to February 2005); and EMBASE (1980 to December 2004).

The following search terms were used for MEDLINE and CENTRAL and adapted for EMBASE. The search terms used in MEDLINE were combined with the highly sensitive strategy devised by Dickersin (Dickersin 1994).

MEDLINE

1 exp MYCOPLASMA/
2 exp Mycoplasma pneumoniae/
3 mycoplasma
4 or/1-3
5 exp BRONCHITIS/
6 exp PNEUMONIA/
7 exp Respiratory Tract Infections/
8 bronchitis
9 pneumonia
10 atypical pneumonia
11 respiratory tract infection$
12 acute respiratory infection$
13 or/5-12
14 exp Anti-Bacterial Agents/
15 exp MACROLIDES/
16 exp QUINOLONES/
17 exp TETRACYCLINES/
18 antibiotic$
19 (macrolide$ or erythromycin or roxithromycin or clarithromycin or azithromycin)
20 or/14-19
21 exp CHILD/
22 (child or children)
23 (paediatric or pediatric)
24 or/21-23
25 4 and 13 and 20 and 24

There were no language restrictions.

Searching other resources

We checked all references for reports of trials.

Data collection and analysis

Selection of studies

Retrieval of studies: From the title, abstract or descriptions, we independently reviewed literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text using specific criteria, we independently selected trials for inclusion. We measured agreement using the kappa statistic and resolved disagreement by consensus.

Data extraction and management

We independently extracted data and resolved disagreement by consensus. Trials that satisfied the inclusion criteria were reviewed and the following information recorded: study setting; year of study; source of funding; patient recruitment details (including number of eligible children); inclusion and exclusion criteria; randomisation and allocation concealment method; numbers of participants randomised; blinding (masking) of participants, care providers and outcome assessors; intervention (type of anti-microbials, dose, duration); control (type, dose, duration); co-interventions; numbers of patients not followed up; reasons for withdrawals from study protocol (clinical, side-effects, refusal and other); details on side-effects of therapy; and whether intention-to-treat analyses were possible. Data were extracted on the outcomes described previously. We requested further information from the study authors where required.

Assessment of risk of bias in included studies

We independently assessed the quality of studies included in the review. Four components of quality were assessed:

1. Allocation concealment. Trials will be scored as: Grade A: Adequate concealment; Grade B: Unclear; Grade C: Clearly inadequate concealment (Grade A = high quality).

2. Blinding. Trials will be scored as: Grade A: Participant and care provider and outcome assessor blinded; Grade B: Outcome assessor blinded; Grade C: Unclear; Grade D: No blinding of outcome assessor (Grade A, B = high quality).
3. Reporting of participants by allocation group. Trials will be scored as: Grade A: The progress of all randomised children in each group described; Grade B: Unclear or no mention of withdrawals or dropouts; Grade C: The progress of all randomised children in each group clearly not described (Grade A = high quality).
4. Follow up. Trials will be scored as: Grade A: Outcomes measured in more than 90% (where withdrawals due to complications and side-effects are categorised as treatment failures); Grade B: Outcomes measured in 80 to 90%; Grade C: Unclear; Grade D: Outcomes measured in less than 80% (Grade A = high quality).
While only the allocation concealment quality is displayed in the meta-analysis figures, all assessments were included in the table 'Characteristics of included studies'. Inter-author reliability for the identification of high quality studies for each component was measured by the kappa statistic.
Each study was assessed using a one to five scale described by Jadad (Jadad 1996) and summarised as follows:

- Was the study described as randomised? (1 = yes; 0 = no)
- Was the study described as double blind? (1 = yes; 0 = no)
- Was there a description of withdrawals and dropouts? (1= yes; 0 = no)
- Was the method of randomisation clearly described and appropriate? (1= yes; 0 = no)
- Was the method of double blinding well described and appropriate? (1= yes; 0 = no)

Unit of analysis issues

In the protocol it was planned to calculate relative and absolute risk reductions using an intention-to-treat analysis for the dichotomous outcome variables of each individual study. However, data were unavailable.
In the protocol it was planned to include the results from studies that met the inclusion criteria and report any of the outcomes of interest in the subsequent meta-analysis. It was planned to calculate the summary weighted risk ratio and 95% confidence interval (CI) (fixed effect model) using the inverse of the variance of each study result for weighting (Cochrane statistical package, Review Manager 4.2). It was planned to calculate the number - needed -to treat using the summary odds ratio and the average control event rate described in the relevant studies. It was stated in the protocol that the cough indicies were assumed to be normally distributed continuous variables so the mean difference in outcomes could be estimated (weighted mean difference). In studies that reported outcomes using different measurement scales, the standardised mean difference would be estimated. However, data were unavailable.
In the protocol it was planned to describe any heterogeneity between the study results and, depending upon the number of trials included in the review, a funnel plot was planned to look for publication bias. However, data were unavailable and no studies were included in a meta-analysis.
In the protocol it was intended to perform an a priori subgroup analysis for:

1. children aged seven years and older;
2. intervention type (class of antibiotics);
3. diagnostic criteria used for identification of *M. pneumoniae.*

However, data were unavailable.
In the protocol a sensitivity analyses was planned to assess the impact of the potentially important factors on overall outcomes:

1. study quality;
2. study size;
3. variation in the inclusion criteria;
4. differences in the medications used and duration of treatment in the intervention and comparison groups;
5. differences in outcome measures;
6. analysis by 'treatment received' rather than 'intention-to treat'.

However, data were unavailable.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The initial search identified 91 potentially relevant titles. After reviewing the abstracts, 17 papers in full text were obtained for consideration of inclusion into the review. Ten papers were excluded and details are provided in the table 'Characteristics of excluded studies'. The main reasons for exclusion were the non-randomised nature of the study (Jensen 1967; Sakata 2001; Vasilos 1995) or use of inadequate placebo or comparator (Block 1995; Chien 1993; Jensen 1967; Manfredi 1992; Nogeova 1997; Ronchetti 1994; Schonwald 1990; Yin 2002). Three of the excluded studies were non-English - Japanese (Sakata 2001), Russian (Vasilos 1995) and Chinese (Yin 2002). Seven studies were included and details are provided in the table 'Characteristics of included studies'. Three of the included studies were non-English - German (Ruhrmann 1982) and Spanish (Gomez Campdera 1996; Saez-Llorens 1998).

Included studies

Participants

The studies involved children diagnosed with LRTI ranging in age from 1 month to 16 years. In all except two studies (Gomez Campdera 1996; Soderstrom 1991) children had pneumonia supported with abnormal chest x-ray and apart from the study by Ruhrmann 1982 the children were described as having community acquired pneumonia. The study by Gomez Campdera 1996 did not define pneumonia and the study by Soderstrom 1991 included patients with acute bronchitis. The number of children with *M. pneumoniae* was not stated in three studies (Gomez Campdera 1996; Ruhrmann 1982; Saez-Llorens 1998). In one study (Wubbel 1999) there were 12 children with *M. pneumoniae* infections and 6 were in the subgroup randomised to either azithromycin or amoxycillin-clavulanate, but the number assigned to each therapy was not available. In two other studies the number of children with *M. pneumoniae* infections in each intervention group was provided - in the study by Harris 1998 there were 30 children who had *M. pneumoniae* infections randomised to either azithromycin or amoxycillin-clavulanate (21 in azithromycin group and 9 in amoxycillin-clavulanate group), and there were eight children in the study by Kogan 2003 (five in azithromycin group and three in amoxycillin-clavulanate group). In the study by Soderstrom 1991 there were only seven patients with lower respiratory tract infections (bronchitis) and one case of *M. pneumoniae*, but the age of the patient with *M. pneumoniae* was not provided.

Interventions

Studies included in this review involved patients with LRTI randomised to either a macrolide antibiotic or another antibiotic, usually a different macrolide or non-macrolide antibiotic. In two studies (Ruhrmann 1982; Soderstrom 1991) the entire study population was randomised to either a macrolide or non-macrolide antibiotic. Ruhrmann 1982 included children with pneumonia who received either erythromycin 70 to 80 mg/kg/day or amoxycillin 60 to 70 mg/kg/day. The duration of therapy was not stated. The study by Soderstrom 1991 had a subgroup of patients (number of children not stated) with acute bronchitis who received either erythromycin 500 mg twice daily for seven days or phenoxymethylpenicillin 800 mg twice daily for seven days. Four studies (Gomez Campdera 1996; Harris 1998; Saez-Llorens 1998; Wubbel 1999) randomised a subgroup of children under five years of age to azithromycin or amoxycillin-clavulanate. The dose of amoxycillin-clavulanate was 40 mg/kd/day in three divided doses for 10 days in all studies. The dose of azithromycin was 10 mg/kg once daily for three days in one study (Gomez Campdera 1996) and 10 mg/kg on day 1 followed by 5 mg/kg once daily for day 2 to 5 in three studies (Harris 1998; Saez-Llorens 1998; Wubbel 1999). In the study by Kogan 2003 the intervention for the subgroup with classic pneumonia was either azithromycin 10 mg/kg once daily for three days or amoxycillin 75 mg/kg/day in three divided doses for seven days.

Outcomes

Clinical response was the main outcome but was not defined in three studies (Gomez Campdera 1996; Ruhrmann 1982; Soderstrom 1991). In three studies clinical cure was defined as complete resolution of symptoms and signs by day 15 to 19 (Harris 1998), day 10 to 25 (Saez-Llorens 1998) and day 10 to 37 (Wubbel 1999). In the study by Kogan 2003 the clinical response was defined as the proportion of children without fever on day 3. Radiological outcome was recorded in three studies (Gomez Campdera 1996; Harris 1998; Kogan 2003) but was not defined in the study by Gomez Campdera 1996. Bacteriological outcome was recorded in two studies (Harris 1998; Saez-Llorens 1998) but was not defined in the study by Saez-Llorens 1998. Adverse events were recorded by four studies (Gomez Campdera 1996; Harris 1998; Saez-Llorens 1998; Wubbel 1999) and were only defined in the study by Harris 1998.

Attempts were made to obtain individual patient data from three studies (Harris 1998; Kogan 2003; Wubbel 1999) where the number of children with *M. pneumoniae* was identified, but no reply was received at the time this review was completed.

Risk of bias in included studies

Jadad scores ranged from 1 to 3, with one study scoring 1 (Gomez Campdera 1996), five studies scoring 2 (Harris 1998; Kogan 2003; Ruhrmann 1982; Saez-Llorens 1998; Wubbel 1999) and one study scoring 3 (Soderstrom 1991). Agreement between the two authors for quality of studies varied with weighted kappa score of 0.18 for Jadad score and 0.49 for quality assessment. A discussion between reviewers on how to interpret the Jadad scoring system did not take place beforehand and this, along with the small numbers involved, was reflected in the low kappa score. The main discrepancy in quality assessment arose with interpretation of allocation concealment and reporting of participants by allocated group. Disagreement in both instances was resolved by consensus.

Randomisation

All studies were described as randomised and the method of randomisation was clearly described and appropriate in two studies (Ruhrmann 1982; Saez-Llorens 1998) where a random number list was used. The method of randomisation was unclear in one study (Wubbel 1999) where the method used was described as a list of randomised therapy assignments. In the study by Soderstrom 1991 the method used was sequential patient numbers and this was thought to be inadequate. Three studies (Gomez Campdera 1996; Harris 1998; Kogan 2003) did not describe the method of randomisation.

Allocation

Concealment of allocation was unclear in all except two studies (Saez-Llorens 1998; Wubbel 1999), where therapy was assigned by pharmacy.

Blinding

There was no blinding in four studies (Gomez Campdera 1996; Ruhrmann 1982; Saez-Llorens 1998; Wubbel 1999). In the remaining three studies the blinding involved only the participant (Harris 1998), clinician (Kogan 2003) or radiologist (Soderstrom 1991).

Effects of interventions

There were 1352 children enrolled from six studies. The number of children from one study (Soderstrom 1991) was unavailable. Data interpretation was significantly limited by the inability to extract data that specifically referred to children with *M. pneumoniae*. There were no studies of children randomised to any antibiotic versus placebo. The included studies comprised a subgroup of children who were randomised to a macrolide versus non-macrolide antibiotic. The total number of children in this subgroup was not known as the numbers were only available in four studies (Harris 1998; Kogan 2003; Ruhrmann 1982; Wubbel 1999). The number of children with LRTI secondary to *M. pneumoniae* in this subgroup was only available in two studies (Harris 1998; Kogan 2003) and the lack of individual patient data did not allow for inclusion of results in a meta-analysis. There was a total of 26 in azithromycin group and 12 in amoxycillin-clavulanate group.

In the study by Gomez Campdera 1996 the rate of clinical cure was 95.12% in the azithromycin group and 90.41% in the amoxycillin-clavulanate group. Radiological improvement was noted in 90.6% of the azithromycin group. Adverse events were recorded in 11.25% of the azithromycin group and 17.14% in the amoxycillin-clavulanate group. Harris 1998 reported no difference in the rate of clinical cure at day 15 to 19 (67.2% versus 66.7%) and four to six weeks (85.1% versus 85.4%) of children randomised to azithromycin or amoxycillin-clavulanate. *M. pneumoniae* was identified in 16% (30 of 188 children under five years of age). Eradication of *M. pneumoniae* occurred in three out of three in the azithromycin group and in none out of one in the amoxycillin-clavulanate group. Adverse events in those children under five years of age were 12.1% in the azithromycin group and 42.3% in the amoxycillin-clavulanate group. One patient in each group discontinued treatment because of adverse events. In the study by Kogan 2003 which compared azithromycin to amoxicillin in children with classical pneumonia (8 children of 47 had *M. pneumoniae*), x-ray resolution was significantly better in those treated with azithromycin (81% versus 60.9% at day 7) but there was no difference in clinical symptoms or signs between groups. In those with atypical pneumonia (23 children of 59 had *M. pneumoniae*) there was no significant difference between children treated with azithromycin or erythromycin (Kogan 2003). Ruhrmann 1982 reported clinical cure after 3.79 days in erythromycin group and 3.96 days in amoxycillin group. Saez-Llorens 1998 reported a similar clinical response (99% versus 98%) in children under five years who were randomised to azithromycin or amoxycillin-clavulanate. Eradication of *M. pneumoniae* occurred in 23 out of 24 in the azithromycin group. Adverse events were reported in 11% on azithromycin, 30% on amoxycillin-clavulanate and 27% on erythromycin. Soderstrom 1991 did not report the clinical response in the subgroup of patients with bronchitis. In the study by Wubbel 1999, where 7% (12 of 168 children) had *M. pneumoniae*, no difference was found in children randomised to azithromycin or amoxicillin-clavulanate. Adverse events were reported in 14% on azithromycin, 67% on amoxycillin-clavulanate and 25% on erythromycin. Eleven patients did not complete the prescribed therapy.

DISCUSSION

Summary of main results

This review failed to find any randomised controlled trials which specifically looked at the effectiveness of antibiotics for LRTI secondary to *M. pneumoniae*. There were no studies of antibiotics versus placebo. In the subgroup of children with LRTI secondary to *M. pneumoniae* the intervention was a macrolide antibiotic versus a non-macrolide antibiotic, usually amoxycillin-clavulanate. This subgroup identified only 38 children with *M. pneumoniae* infection and there were insufficient data to analyse the efficacy of macrolide antibiotics in this group. Adverse events were common, reported in 11% to 67% of children. The majority of adverse events related to the gastrointestinal tract (diarrhoea, vomiting, abdominal pain, nausea, anorexia) and where reported, were more common in younger children (under five years of age).

Quality of the evidence

There were significant difficulties in interpretation of data from the included studies. Firstly, although all studies (except Soderstrom 1991) enrolled children with LRTI, only a proportion had *M. pneumoniae* infection. It was not possible to obtain information on the sub-group with *M. pneumoniae*. Secondly, the dose and type of antibiotics differed among studies. Thirdly, application of diagnostic criteria (serology versus PCR) varied and these are not necessarily interchangeable. Fourthly, the inclusion criteria differed (various types of LRTI manifestation) between studies. Furthermore the outcomes measured were variable and in some papers, clinical cure was undefined.

Despite the commonality of *M. pneumoniae* LRTI in children (up to 40% of CAP reported by Waites 2003), there is surprisingly no RCT that has specifically evaluated the efficacy of antibiotics for the treatment of childhood LRTI secondary to *M. pneumoniae* infections acquired in the community. This is reflected in conflicting advice given in paediatric textbooks (Phelan 1994; Rudolph

2003) and this systematic review has highlighted the need for such studies.

AUTHORS' CONCLUSIONS

Implications for practice

This review found insufficient evidence to draw any conclusions about the efficacy of antibiotics for LRTI secondary to *M. pneumoniae* in children. The use of antibiotics for *M. pneumoniae* LRTI has to be individualised depending on the clinical context (for example setting, clinical history and signs, presence of immunodeficiency etc) and balanced with possible adverse events associated with antibiotic use.

Implications for research

M. pneumoniae infection is relatively common and its clinical manifestations range from being asymptomatic to death from complications of *M. pneumoniae* infection. As respiratory symptoms are the most common symptoms, there is a need for high quality, double-blinded randomised controlled trials to assess the efficacy and safety of antibiotics for LRTI secondary to *M. pneumoniae* in children. Studies should consider the various clinical and microbiological diagnostic criteria of *M. pneumoniae* infection and utilise clear outcome criteria. Community studies using PCR for rapid early diagnosis would be valuable to evaluate the efficacy of antibiotics for *M. pneumoniae* for respiratory and non respiratory manifestations as well as for prevention of complications and microbiological clearance of *M. pneumoniae*.

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REFERENCES

References to studies included in this review

Gomez Campdera 1996 ***{published data only}***
Gomez Campdera JA, Navarro Gomez ML, Hernandez-Sampelayo T, Merello Godino C, Sanchez Sanchez C. Azithromycin in the treatment of ambulatory pneumonia in children. *Acta Pediatrica Espanola* 1996;**54**(8):554–62.

Harris 1998 ***{published data only}***
Harris J-AS, Kolokathis A, Campbell M, Cassell GH, Hammerschlag MR. Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children. *Pediatric Infectious Disease Journal* 1998;**17**(10): 865–71.

Kogan 2003 ***{published data only}***
Kogan R, Martinez MA, Rubilar L, Paya E, Quevedo I, Puppo H, et al.Comparative randomized trial of azithromycin versus erythromycin and amoxycillin for treatment of community-acquired pneumonia in children. *Pediatric Pulmonology* 2003;**35**(2):91–8.

Ruhrmann 1982 ***{published data only}***
Ruhrmann H, Blenk H. Erythromycin versus amoxicillin for the treatment of pneumonia in children. *Infection* 1982; **10**:S86–91.

Saez-Llorens 1998 ***{published data only}***
Saez-Llorens X, Castano E, Wubbel L, Castrejon MM, de Morales I, Vallarino D, et al.Importance of Mycoplasma pneumoniae and Chlamydia pneumoniae in children with community-acquired pneumonia. *Revista Medica de Panama* 1998;**23**(2):27–33.

Soderstrom 1991 ***{published data only}***
Soderstrom M, Blomberg J, Christensen P, Hovelius B. Erythromycin an Phenoxymethylpenicillin (Penicillin V) in the Treatment of Respiratory Tract Infections as Related to Microbiological Findings and Serum C-Reactive Protein. *Scandanavian Journal of Infectious Disease* 1991;**23**:347–54.

Wubbel 1999 ***{published data only}***
Wubbel L, Muniz L, Ahmed A, Trujillo M, Carubelli C, McCoig C, et al.Etiology and treatment of community-acquired pneumonia in ambulatory children. *Pediatric Infectious Disease Journal* 1999;**18**(2):98–104.

References to studies excluded from this review

Block 1995 ***{published data only}***
Block S, Hedrick J, Hammerschlag MR, Cassell GH, Craft JC. Mycoplasma pneumoniae and Chlamydia pneumoniae in pediatric community-acquired pneumonia: Comparative efficacy and safety of clarithromycin vs erythromycin ethylsuccinate. *Pediatric Infectious Disease Journal* 1995;**14** (6):471–7.

Chien 1993 ***{published data only}***
Chien SM, Pichotta P, Siepman N, Chan CK. Treatment of community-acquired pneumonia. A multicenter, double-blind, randomized study comparing clarithromycin with erythromycin. *Chest* 1993;**103**(3):697–701.

Jensen 1967 *{published data only}*

Jensen KJ, Senterfit LB, Scully WE, Conway TJ, West RF, Drummy WM. Mycoplasma pneumoniae infections in children. An epidemiological appraisal in families treated with oxytetracycline. *American Journal of Epidemiology* 1967;**86**(2):419–32.

Manfredi 1992 *{published data only}*

Manfredi R, Jannuzzi C, Mantero E, Longo L, Schiavone R, Tempesta A, et al.Clinical comparative study of azithromycin versus erythromycin in the treatment of acute respiratory tract infections in children. *Journal of Chemotherapy* 1992;**4**(6):364–70.

Nogeova 1997 *{published data only}*

Nogeova A, Galova K, Krizan L, Sufliarska S, Cizmarova E, Raskova J, et al.Ceftibuten vs cefuroxime-axetil in initial therapy for community-acquired bronchopneumonia: Randomized multicentric study in 140 children. *Infectious Diseases in Clinical Practice* 1997;**6**(2):133–4.

Ronchetti 1994 *{published data only}*

Ronchetti R, Blasi F, Grossi E, Pecori A, Bergonzi F, Ugazio A, et al.The role of azithromycin in treating children with community-acquired pneumonia. *Current Therapeutic Research and Clinical Experimentation* 1994;**55**(4):965–70.

Sakata 2001 *{published data only}*

Sakata H. Clinical study on azithromycin in lower respiratory infections in children. *Japanese Journal of Chemotherapy* 2001;**49**(6):363–8.

Schonwald 1990 *{published data only}*

Schonwald S, Gunjaca M, Kolacny-Babic L, Car V, Gosev M. Comparison of azithromycin and erythromycin in the treatment of atypical pneumonia. *Journal of Antimicrobial Chemotherapy* 1990;**25**:123–6.

Vasilos 1995 *{published data only}*

Vasilos LV, Rumel NB, Shchuka SS. Chemotherapeutic effectiveness of erythromycin, rifampicin and tetracyclines in chlamydiosis and mycoplasmosis in children. *Antibiotiki i Khimiterapiia* 1995;**40**(6):40–2.

Yin 2002 *{published data only}*

Yin T, Jiang Y-F. Comparison of azithromycin and erythromycin in the treatment of pediatric mycoplasmal pneumonia. *Chinese Journal of Antibiotics* 2002;**27**(4): 240–2.

Additional references

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286–91.

Jadad 1996

Jadad A, Moore R, Carroll D, Jenkinson C, Reynolds D, Gavaghan D, et al.Assessing the quality of reports of randomised clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**(1):1–12.

Katz 1998

Katz SL, Gershon AA, Hoetz PJ. *Krugman's Infectious Disease of Children*. 10th Edition. USA: Mosby, 1998.

Michelow 2004

Michelow IC, Olsen K, Lozano J, Rollins NK, Duffy LB, Ziegler T, et al.Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. *Pediatrics* 2004;**113**(4):701–7.

Murray 2003

Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Yolken RH. *Manual of Clinical Microbiology*. 8th Edition. Vol. **1**, Washington DC: ASM Press, 2003.

Nelson 2002

Nelson CT. Mycoplasma and Chlamydia pneumonia in pediatrics. *Seminars in Respiratory Infections* 2002;**17**(1): 10–4.

Phelan 1994

Phelan PD, Olinsky A, Robertson CF. *Respiratory Illness in Children*. 4th Edition. Oxford: Blackwell Scientific Publications, 1994.

Principi 2001

Principi N, Esposito S. Emerging role of Mycoplasma pneumoniae and Chlamydia pneumoniae in paediatric respiratory-tract infections. *The Lancet Infectious Diseases* 2001;**1**:334–44.

Principi 2002

Principi N, Esposito S. Mycoplasma pneumoniae and Chlamydia pneumoniae cause lower respiratory tract disease in paediatric patients. *Current Opinion in Infectious Diseases* 2002;**15**(3):295–300.

Rudolph 2003

Rudolph CD, Rudolph AM, Hostetter MK, Lister G, Siegel NJ. *Rudolph's Pediatrics*. 21st Edition. USA: McGraw-Hill Medical Publishing Division, 2003.

Waites 2003

Waites KB. New Concepts of Mycoplasma pneumoniae infections in children. *Pediatric Pulmonology* 2003;**36**: 267–78.

Wubbel 1999

Wubbel L, Muniz L, Ahmed A, Trujillo M, Carubelli C, McCoig C, et al.Etiology and treatment of community-acquired pneumonia in ambulatory children. *Pediatric Infectious Disease Journal* 1999;**18**:98–104.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gomez Campdera 1996

Methods	Patients were recruited from emergency department with a diagnosis of pneumonia for the periods 1 May 1994 to 30 April 1995 and 1 December 1995 to 30 June 1996. Inclusion and exclusion criteria were not stated. Study participants were randomised to azithromycin or either amoxycillin-clavulanate if under 5 years and erythromycin if over 5 years. The method of randomisation was not described. The study was not blinded. There was no description of withdrawals or dropouts. There was no assessment of compliance. Clinical outcomes were evaluated on day 3, 10 and 30, and chest x-ray was repeated on day 30. Outcomes measures included clinical response, hospitalisation, radiological improvement and adverse events. Clinical response was classified as unchanged, improved, cured or worse. These categories were not defined. Radiological improvement at day 30 was not defined Assessment of Quality 1. Allocation concealment: Grade B 2. Blinding: Grade D 3. Reporting of participants by allocation group: Grade B 4. Follow up: Grade C Jadad Score: 1
Participants	155 children aged 6 months to 16 years with pneumonia. Males = 84. Number of children with M. pneumoniae infection in each group not stated
Interventions	Group A (n = 82): azithromycin 10 mg/kg/day OD for 3 days. Group B (n = 73): amoxycillin-clavulanate 40 mg/kg/day TID for 10 days if under 5 years and erythromycin 40 mg/kg/day TID for 10 days if over 5 years
Outcomes	1.Clincial 2. Radiological 3. Adverse events
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Harris 1998

Methods	Patients were recruited from 23 centres with a diagnosis of community acquired pneumonia from 31 January 1994 to 31 May 1995. Inclusion criteria were children with clinically suspected pneumonia based on a radiological finding and the presence of tachyapnoea. In addition patients had at least one of the following: fever or history of fever within 24 hours, cough, WCC >= 12000/mm, or chest findings suggestive of pneumonia. Exclusion criteria were hypersensitivity to macrolides, penicillin or beta-lactam antibiotics, pregnancy or lactation, parenteral therapy required because of severe or multilobar pneumonia, treatment with any other systemic antibiotics within enrolment, evidence of underlying haematological, renal, hepatic or cardiovascular disease, chronic steroid use or concomitant treatment with theophylline, carbamazine, ergotamine, digitalis glycosides, terfenadine, loratadine or astemizole. Study was a multicentre, parallel group in which participants were randomised 2:1 to azithromycin or either amoxycillin-clavulanate if under 5 years and erythromycin if over 5 years. The method of randomisation was not described. Participants were blinded to therapy but there was no mention of blinding of clinicians or outcome assessors. There was a description of withdrawals or dropouts. There was an assessment of compliance by comparing medication bottle weights at beginning and end of study. Patients were evaluated at four clinic visits: baseline; study days 2 to 5; study days 15-19; and 4-6 weeks post therapy. Laboratory tests were obtained at baseline and on Study days 15-19. Chest x-rays were obtained at baseline and 4-6 weeks post-therapy. Evidence of infection with M. pneumoniae was determined by enzyme-linked immunosorbent assay and defined as either single positive serum IgM (>= 1:10) or 4-fold increase in IgG titre. Clinical response at study days 15 to 19 was classified as: cure, complete resolution of signs and symptoms of pneumonia; improvement, incomplete resolution of signs and symptoms of pneumonia; failure, persistence (or progression) of signs and symptoms of pneumonia after 3 days of therapy or development of new clinical findings consistent with active infection or persistence (or progression) of radiological findings obtained when clinically indicated. Clinical response 4 to 6 weeks post-therapy was classified as follows: cure; complete resolution of signs and symptoms of pneumonia and improvement or resolution of radiographic findings; failure; persistence (or progression) of signs and symptoms of pneumonia after 3 days of therapy or development of new clinical findings consistent with active infection or persistence (or progression) of radiological findings. Bacteriological response was classified as follows: eradication (presumed or proven), elimination of the original organism from the same site during or after completion of therapy and includes cases where repeat specimens were nor obtained and patients considered a clinical cure or improved; persistence, failure to eradicate the organism and includes cases where specimens were not obtainable at the time alternative therapy was instituted and the patient was considered a clinical failure. Adverse events were monitered throughout the study by reported symptoms, physical examinations and laboratory tests. Events were rated by severity (mild, moderate or severe at the discretion of the investigator), organ system and relation to study drug Assessment of Quality 1. Allocation concealment: Grade B 2. Blinding: Grade C 3. Reporting of participants by allocation group: Grade A 4. Follow up: Grade B Jadad Score: 2
Participants	456 children aged 6 months to 15 years with CAP were enrolled. 36 patients (25 in azithromycin group and 11 in comparator group) were excluded for methodologic reasons leaving 420 patients (285 in azithromycin and 135 in comparator group) available for analysis. Six children discontinued treatment because of adverse events. Males = 236. The number of children with M. pneumoniae in the group randomised to macrolide versus non-macrolide (i.e. children < 5 years) was 30 with 21 in azithromycin group and 9 in amoxycillin-clavanulate group

Harris 1998 (*Continued*)

Interventions	Children under 5 years only - Group A (n = 125): azithromycin 10 mg/kg OD day 1, 5 mg/kg OD day 2 to 5, and placebo day 1 to 10. Group B (n = 63): amoxycillin-clavulanate 40 mg/kg TDS day 1 to 10 and placebo day 1 to 5
Outcomes	1. Clinical 2. Radiological 3. Bacteriological 4. Adverse events
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Kogan 2003

Methods	Patients with a diagnosis of community acquired pneumonia were recruited from 1 January 1996 to 1 January 1999. Inclusion criteria were children with a clinical diagnosis radiologically confirmed of presumed bacterial community acquired pneumonia, eligible for treatment with oral antibiotics and without signs of respiratory insufficiency. Exclusion criteria were history or evidence of chronic pathology of any organ system, chronic pulmonary disease, history of prematurity, treatment with any antibiotics within 5 days prior to enrolment, or known hypersensitivity to beta-lactam antibiotics or macrolides. The study population was divided into two groups according to clinical and radiological patterns. One group included those children who presented with signs of classic bacterial pneumonia, with high fever and chest findings of crackles or signs of consolidation, and chest x-rays with segmental, alveolar, or lobar consolidation. The second group included patients with atypical pneumonia, with prominent and frequently paroxysmal cough, variable fever, few clinical signs of consolidation, crackles and wheezing, and chest x-rays with a mixed alveolar-interstitial pattern. Participants with classic pneumonia were randomised to either amoxycillin or azithromycin, whereas patients in the atypical pneumonia were randomly assigned to either azithromycin or erythromycin. The method of randomisation was not described. There was no mention of blinding except for blinding of the radiologist who viewed follow up chest x-rays done on study days 7 and 14. There was a description of withdrawals or dropouts. There was no assessment of compliance. Outcomes were evaluated at three clinic visits, on study days 3, 7 and 14. A chest x-ray was done in each child on study days 7 and 14. Evidence of infection was determined by indirect immunofluorescence (IFI) and enzyme-linked immunosorbent assay to test sera for IgM antibiodies to M pneumoniae. An antibody titre > 1:16 on a single first serum specimen was considered positive for IFI. Clinical Response in the classic pneumonia group was defined as proportion of children without fever on day 3 and/or improvement of more than 75% of radiographic baseline findings on study day 7 Assessment of Quality 1. Allocation concealment: Grade B 2.Blinding: Grade C 3. Reporting of participants by allocation group: Grade A 4. Follow-up: Grade B Jadad Score: 2
Participants	110 children aged 1 month to 14 years were enrolled. 4 children developed serious pneumonia in the first 12 hours of enrolment and were excluded from the study (3 from the atypical group and 1 from the classic group). The remaining 106 completed the study. The mean age was 4.9 years and 53 were male. 47 met the criteria for classic pneumonia. The number of children with M. pneumoniae in the classic group was 8, with 5 in azithromycin group and 3 in amoxycillin-clavanulate group
Interventions	Patients with classic pneumonia: Group A (n = 23): azithromycin 10 mg/kg OD for 3 days. Group B (n = 24): amoxycillin 75 mg/kg/day in 3 divided doses for 7 days
Outcomes	1. Clinical 2. Radiological
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ruhrmann 1982

Methods	Patients were recruited from emergency departments in Dallas and Panama with a diagnosis of community acquired pneumonia for the period February 1996 to December 1997. Inclusion criteria were tachyapnoea, fever, cough, crackles and CXR with changes compatible with pneumonia. Exclusion criteria were hypersensitivity to macrolides or beta-lactam antibiotics, pregnancy, nosocomial pneumonia, use of systemic antibiotics 72 hours prior to recruitment, chronic illness such as HIV, malignancy, cystic fibrosis, haematologic, renal, cardiovascular, hepatic or pulmonary diseases, as well as patients on teofilin, antihistamines, steroids or any medications with potential interaction with macrolides. Study participants were randomised to azithromycin or either amoxycillin-clavulanate if under 5 years and erythromycin if over 5 years. A random number list was used and therapy assigned by pharmacy. The study was not blinded. There was a description of withdrawals or dropouts. There was no assessment of compliance. Clinical outcomes were evaluated on day 2-3 and 10-25. Evidence of infection with M. pneumoniae was defined as either single positive serum IgM (>1:16), 4-fold increase in IgG titre or positive PCR. Outcomes measures included clinical response, hospitalisation, and eradication of M. pneumoniae. Clinical response was classified as clinical cure or fail. Cure was defined as complete resolution or evident improvement of all clinical symptoms and signs, and fail was defined as persistent or progression of symptoms after 3 days of treatment. Eradication of M. pneumoniae was not defined Assessment of Quality 1. Allocation concealment: Grade A 2. Blinding: Grade D 3. Reporting of participants by allocation group: Grade B 4. Follow up: Grade C Jadad Score: 2
Participants	120 children aged 6 months to 14 years with pneumonia. Gender ratio not stated. Number of children with M. pneumoniae infection in each group not stated
Interventions	Group A: erythromycin 70 to 80 mg/kg/day. Duration of therapy not stated. Group B: amoxycillin 60 to 70 mg/kg/day. Duration of therapy not stated
Outcomes	1. Clinical
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Saez-Llorens 1998

Methods	Patients were recruited from emergency departments in Dallas and Panama with a diagnosis of community acquired pneumonia for the period February 1996 to December 1997. Inclusion criteria were tachyapnoea, fever, cough, crackles and CXR with changes compatible with pneumonia. Exclusion criteria were hypersensitivity to macrolides or beta-lactam antibiotics, pregnancy, nosocomial pneumonia, use of systemic antibiotics 72 hours prior to recruitment, chronic illness such as HIV, malignancy, cystic fibrosis, haematologic, renal, cardiovascular, hepatic or pulmonary diseases, as well as patients on teofilin, antihistamines, steroids or any medications with potential interaction with macrolides. Study participants were randomised to azithromycin or either amoxycillin-clavulanate if under 5 years and erythromycin if over 5 years. A random number list was used and therapy assigned by pharmacy. The study was not blinded. There was a description of withdrawals or dropouts. There was no assessment of compliance. Clinical outcomes were evaluated on day 2-3 and 10-25 Clinical outcomes were evaluated on Group A: erythromycin 70 to 80 mg/kg/day. Duration of therapy not stated. Group B: amoxycillin 60 to 70 mg/kg/day. Duration of therapy not stated.day 2-3 and 10-25. Evidence of infection with M. pneumoniae was defined as either single positive serum IgM (>1:16), 4-fold increase in IgG titre or positive PCR. Outcomes measures included clinical response, hospitalisation, and eradication of M. pneumoniae. Clinical response was classified as clinical cure or fail. Cure was defined as complete resolution or evident improvement of all clinical symptoms and signs, and fail was defined as persistent or progression of symptoms after 3 days of treatment. Eradication of M. pneumoniae was not defined Assessment of Quality 1. Allocation concealment: Grade A 2. Blinding: Grade D 3. Reporting of participants by allocation group: Grade B 4. Follow up: Grade C Jadad Score: 2
Participants	Total of 335 children aged 6 months to 15 years with CAP - 168 from Dallas with 106 under 5 years (males = 92) and 167 from Panama with 142 under 5 years (males = 98). Thirty-nine children dropped out. Number of children with M. pneumoniae infection in each group not stated
Interventions	Group A: azithromycin 10 mg/kg on day 1 and 5mg/kg OD for days 2 to 5. Group B: amoxycillin-clavulanate 40 mg/kg/day TID for 10 days if under 5 years and erythromycin 40 mg/kg/day TID for 10 days if over 5 years
Outcomes	1. Clinical 2. Bacteriological 3. Adverse events
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Soderstrom 1991

Methods	Patients aged > 10 years were recruited with any of the following diagnoses: sinusitis, tonsillitis, purulent nasopharyngitis or bronchitis. Inclusion criteria defined acute bronchitis by the presence of at least 4 of the following 5 criteria: (a) cough; (b) increased amounts of sputum; (c) rhonchus; (d) leucocytosis (> 10 x 10 9 leucocytes/l); and (e) temperature > 38 degrees C. Exclusion criteria were allergies to erythromycin or penicillin, those treated with steroids, theophylline or antibiotics within 10 days preceding consultation. The patients in each diagnosis group were randomly assigned to treatment with erythromycin capsules or phenoxymethylpenicillin tablets. The patients were given sequential patient numbers, which indicated which of the two treatments should be given to each patient. The physician at the first visit and the nurse who met the patient at follow up visits were blinded to the intervention. There is no mention of whether the patient was blinded to intervention. There was a description of withdrawals or dropouts. Compliance was assessed by analysing urine sample collected during treatment (days 3-7). The patients kept a daily record of symptoms and were reviewed by nurse 10 to 12 days after their initial visit. Evidence of M. pneumoniae infection was made on the basis of four-fold rise in antibody titre. Outcome measures included clinical response and adverse reactions. Clinical response was classified as asymptomatic, minor symptoms, Streptococcal relapse/re-infection and treatment failure. These clinical outcomes were not defined Assessment of Quality 1. Allocation concealment: Grade B 2. Blinding: Grade B 3. Reporting of participants by allocation group: Grade A 4. Follow up: Grade A Jadad Score: 3
Participants	138 patients were recruited with age range 10 to 70 years (median 32.5). Males = 56. Two patients dropped out. There were only 7 with bronchitis (lower respiratory tract infection) and M. pneumoniae was identified in 1 case
Interventions	Group A: erythromycin 500 mg twice daily for 7 days. Group B: penicillin V 800 mg twice daily for 7 days.
Outcomes	1. Clinical
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wubbel 1999

Methods	Patients were recruited from emergency clinic Children's Medical Centre Dallas, Texas with a diagnosis of community acquired pneumonia from February 1996 to December 1997. Inclusion criteria were children with tachypnoea, fever, cough or rales and an abnormal chest x-ray consistent with pneumonia and considered to have community acquired infection. Exclusion criteria were hypersensitivity to macrolides or beta-lactam antibiotics, pregnancy or lactation, nosocomial acquired infections, hospitalisation, systemic antibiotic within 72 hours before enrollment, cefixime or ceftriaxone within the previous 7 days and chronic diseases. Patients were also excluded if they were receiving medications that had potential adverse interactions with erythromycin or azithromycin. Study participants were randomised to azithromycin or either amoxycillin-clavulanate if under 5 years and erythromycin if over 5 years. A list of randomised therapy assignments was used by research pharmacist to provide patients with either azithromycin, amoxycillin-clavulanate or erythromycin. There was no mention of blinding of participants, clinicians or outcome assessors except radiologists who reviewed all radiographs and were not familiar with the patient's clinical history or results of special studies. There was a description of withdrawals or dropouts. There was an assessment of compliance by measuring the volume of drug in the bottle at 2 to 5 week visit. Clinical evaluation occurred at enrolment, 2 to 3 days and 10 to 37 days after start of therapy. At day 2 to 3 a telephone call was made to the caregiver to assess symptoms, interventions and adverse reactions. Patients were assessed at Weeks 2 to 5 for symptoms, adverse reactions and outcome. At this assessment bacteriological samples were collected - nasopharyngeal and pharyngeal swabs for culture and PCR and serum for convalescent antibody titres. A chest x-ray was repeated only if a patient had signs of persistent or new infection. Clinical response was defined as: cure, resolution of all signs and symptoms; improvement, incomplete resolution of all signs and symptoms; and failure, persistence or progression after 3 days of therapy, new clinical findings suggesting active infection or death related to pneumonia. Bacteriological response was not defined. Adverse events were monitored throughout the study. Evidence of infection with M. pneumoniae was determined by serology (enzyme-linked immunosorbent assay), and culture or PCR from nasopharyngeal swabs. Positive serology was defined as either single positive serum IgM (>= 1: 10) or 4-fold increase in IgG titre Assessment of Quality 1. Allocation concealment: Grade A 2. Blinding: Grade D 3. Reporting of participants by allocation group: Grade A 4. Follow up: Grade B Jadad Score: 2
Participants	174 children aged 6 months to 16 years with CAP were enrolled. Six patients were excluded because of normal chest x-rays. Twenty-one children were excluded from clinical evaluation; 10 failed to return for follow up examination and 11 did not complete treatment. Gender ratio was not mentioned. The total number of children with M. pneumoniae was 12. However, it was not possible to determine how many children with M. pneumoniae were in the group < 5 years who were randomised to either azithromycin or amoxycillin-clavulanate because of lack of individual patient data
Interventions	Children under 5 years only - Group A (n = 39): azithromycin 10 mg/kg OD day 1, followed by 5 mg/kg OD day 2 to 5. Group B (n = 49): amoxycillin-clavulanate 40 mg/kg TDS day 1 to 10
Outcomes	1. Clinical 2. Adverse events
Notes	
Risk of bias	

Wubbel 1999 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

n = number
OD = daily
TID = three times a day
CXR = chest x-ray
PCR = polymerase chain reaction

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Block 1995	Inappropriate intervention. Comparison between two drugs from macrolide group - clarithromycin versus erythromycin ethylsuccinate
Chien 1993	Inappropriate intervention. Comparison between two drugs from macrolide group - clarithromycin versus erythromycin
Jensen 1967	Inappropriate intervention and study not randomised. Study looked at treatment of all affected individuals with oxytetracycline and there was no placebo group. Household contacts were treated with either oxytetracycline or placebo to determine effectiveness of oxytetracycline in secondary prevention of mycoplasma infections. Allocation of treatment of household contacts was not randomised
Manfredi 1992	Inappropriate intervention. Comparison between two drugs from macrolide group - azithromycin versus erythromycin
Nogeova 1997	Inappropriate intervention. Comparison between two drugs from cephalosporin group - ceftibuten versus cefuroxime-axetil
Ronchetti 1994	Inappropriate intervention. Comparison between two drugs from macrolide group - azithromycin versus josamycin
Sakata 2001	Study participants were not randomised.
Schonwald 1990	Inappropriate intervention. Comparison between two drugs from macrolide group - azithromycin versus erythromycin
Vasilos 1995	Study participants were not randomised.
Yin 2002	Inappropriate intervention. Comparison between two drugs from macrolide group - oral azithromycin versus intravenous erythromycin

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 20 May 2005.

Date	Event	Description
22 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 3, 2005

CONTRIBUTIONS OF AUTHORS

JG wrote the protocol, independently selected papers for inclusion, assessed quality and extracted data, and wrote review.

AC edited and co-wrote protocol, independently selected papers for inclusion, assessed quality and extracted data, and edited and co-wrote review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- West Moreton Health Service District, Ipswich, Australia.
- Royal Children's Hospital, Brisbane, Australia.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Mycoplasma pneumoniae; Anti-Bacterial Agents [*therapeutic use]; Bronchitis [*drug therapy; microbiology]; Community-Acquired Infections [drug therapy; microbiology]; Pneumonia, Mycoplasma [*drug therapy]

MeSH check words

Child; Humans